Epigenetic Modulation of miR-122 Facilitates Human Embryonic Stem Cell Self-Renewal and Hepatocellular Carcinoma Proliferation.

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Public Summary:
The self-renewal capacity ascribed to hESCs is paralleled in cancer cell proliferation, suggesting that a common network of genes may facilitate the promotion of these traits. However, the molecular mechanisms that are involved in regulating the silencing of these genes as stem cells differentiate into quiescent cellular lineages remain poorly understood. Here, we show that a differentiated cell specific miR-122 exemplifies this regulatory attribute by suppressing the translation of a gene, Pkm2, which is commonly enriched in hESCs and liver cancer cells (HCCs), and facilitates self-renewal and proliferation. Through a series of gene expression analysis, we show that miR-122 expression is highly elevated in quiescent human primary hepatocytes (hPHs) but lost or attenuated in hESCs and HCCs, while an opposing expression pattern is observed for Pkm2. Depleting hESCs and HCCs of Pkm2, or overexpressing miR-122, leads to a common deficiency in self-renewal and proliferation. Likewise, during the differentiation process of hESCs into hepatocytes, a reciprocal expression pattern is observed between miR-122 and Pkm2. An examination of the genomic region upstream of miR-122 uncovered hyper-methylation in hESCs and HCCs, while the same region is de-methylated and occupied by a transcription initiating protein, RNA polymerase II (RNAPII), in hPHs. These findings indicate that one possible mechanism by which hESC self-renewal is modulated in quiescent hepatic derivatives of hESCs is through the regulatory activity of a differentiated cell-specific miR-122, and that a failure to properly turn “on” this miRNA is observed in uncontrollably proliferating HCCs.

Scientific Abstract:
The self-renewal capacity ascribed to hESCs is paralleled in cancer cell proliferation, suggesting that a common network of genes may facilitate the promotion of these traits. However, the molecular mechanisms that are involved in regulating the silencing of these genes as stem cells differentiate into quiescent cellular lineages remain poorly understood. Here, we show that a differentiated cell specific miR-122 exemplifies this regulatory attribute by suppressing the translation of a gene, Pkm2, which is commonly enriched in hESCs and liver cancer cells (HCCs), and facilitates self-renewal and proliferation. Through a series of gene expression analysis, we show that miR-122 expression is highly elevated in quiescent human primary hepatocytes (hPHs) but lost or attenuated in hESCs and HCCs, while an opposing expression pattern is observed for Pkm2. Depleting hESCs and HCCs of Pkm2, or overexpressing miR-122, leads to a common deficiency in self-renewal and proliferation. Likewise, during the differentiation process of hESCs into hepatocytes, a reciprocal expression pattern is observed between miR-122 and Pkm2. An examination of the genomic region upstream of miR-122 uncovered hyper-methylation in hESCs and HCCs, while the same region is de-methylated and occupied by a transcription initiating protein, RNA polymerase II (RNAPII), in hPHs. These findings indicate that one possible mechanism by which hESC self-renewal is modulated in quiescent hepatic derivatives of hESCs is through the regulatory activity of a differentiated cell-specific miR-122, and that a failure to properly turn "on" this miRNA is observed in uncontrollably proliferating HCCs.